

Is It Diabetic Nephropathy? (When to Biopsy?)

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Nephrology Specialist

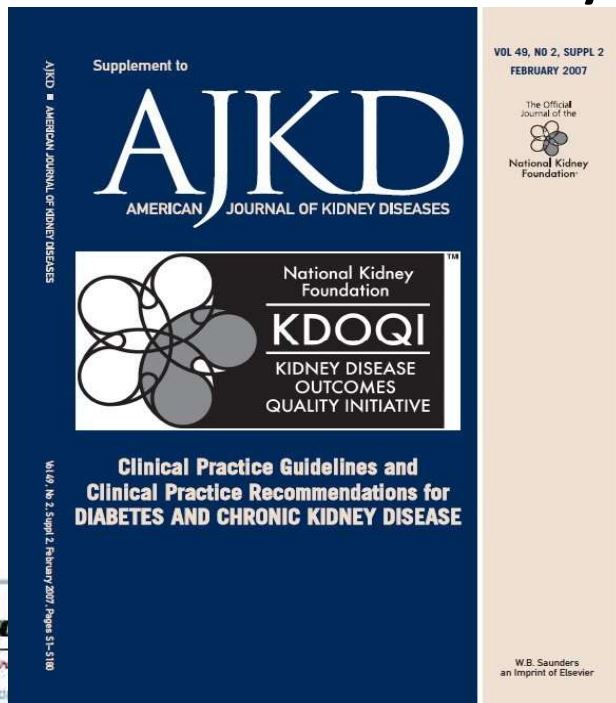
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IMPORTANT MESSAGE



- Renal diseases in diabetic patients are **NOT ALWAYS** due to diabetic nephropathy and even it may not be due to DM.



Terminology for the Kidney Disease of Diabetes

GUIDELINE 1: SCREENING AND DIAGNOSIS OF DIABETIC KIDNEY DISEASE

Guideline 1: Screening and Diagnosis of DKD

CKD in patients with diabetes may or may not represent DKD. In the absence of an established diagnosis, the evaluation of patients with diabetes and kidney disease should include investigation into the underlying cause(s).

The term diabetic glomerulopathy should be reserved for biopsy-proven kidney disease caused by diabetes.



Renal & Urological Problems that may be presented in Diabetics

Pathological Diagnoses other than Diabetic Nephropathy

When to suspect other cause rather than DN?

Is it DN?

When to biopsy?

0 | FSGS | MCD | Pauci | MGN | SLE | IgAN | Mes | Other |
Pathologic diagnoses

Any other glomerular disease
not related to DM

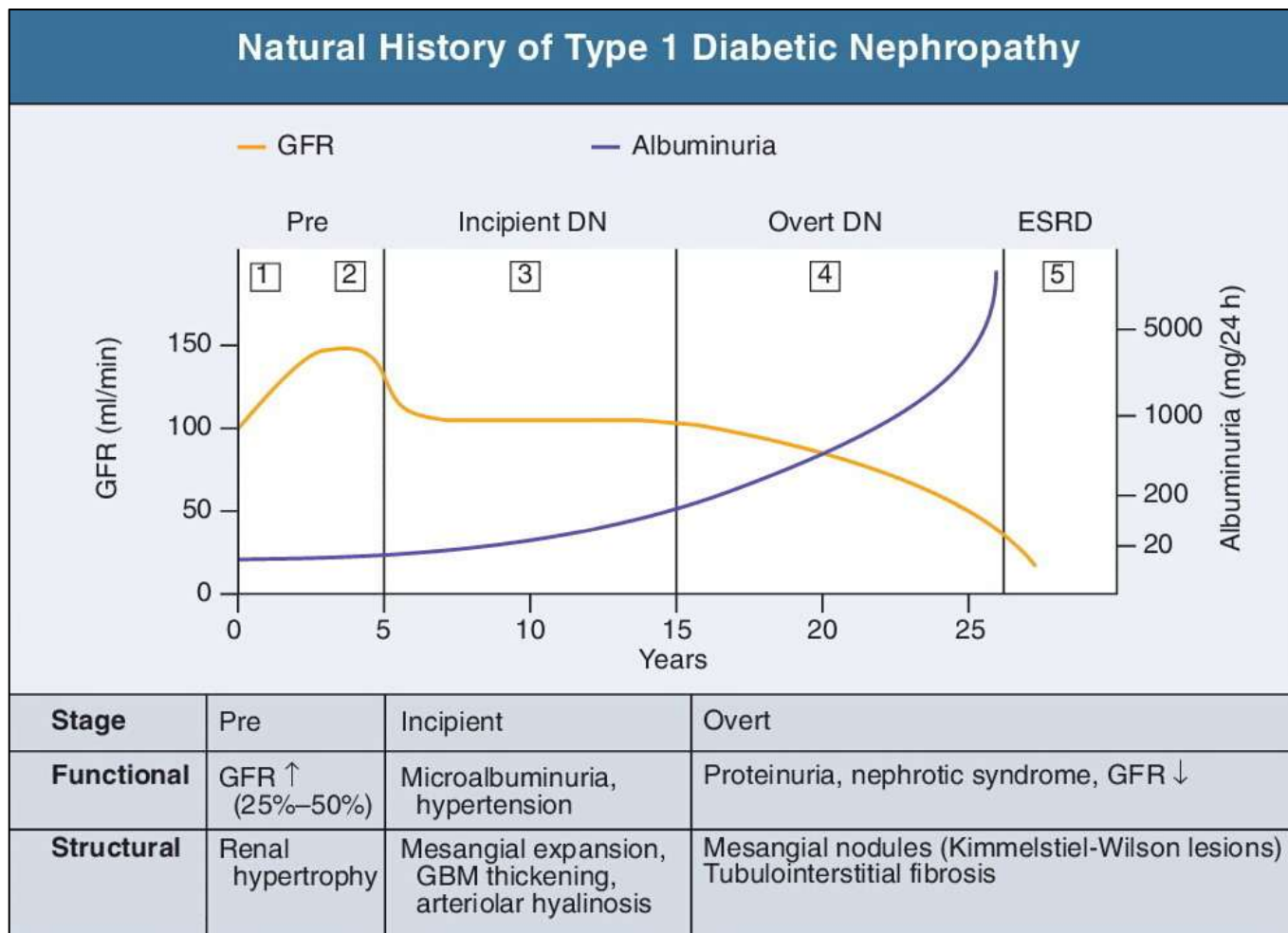
Is it Diabetic Nephropathy?

You have to answer the following

1. What is the type of DM?
2. Is there an evidence of Diabetic retinopathy?

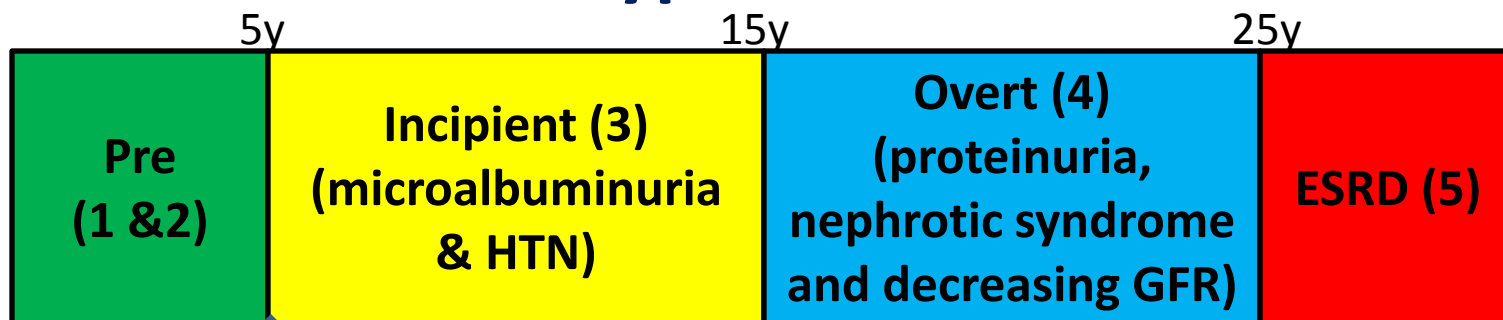
Diabetic Nephropathy & Diabetic Retinopathy

Type 1 DM



Diabetic Nephropathy & Diabetic Retinopathy

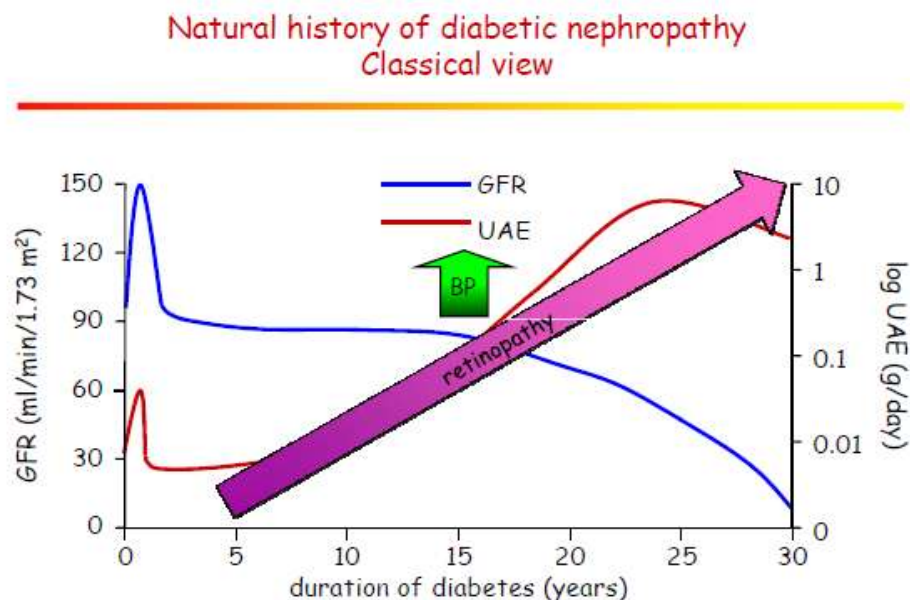
Type 1 DM



At 5 years from onset of DM type 1, nephropathy coincides with retinopathy

Diabetic retinopathy is present in virtually all patients with type 1 diabetes and nephropathy *

So if nephropathy is evident in absence of retinopathy in Type 1 DM



Krolewski AS et al, Am J Med 1985; 78:785-794

Diabetic Nephropathy & Diabetic Retinopathy

Type 2 DM

Only 50% to 60% of proteinuric patients with type 2 diabetes suffer from retinopathy. **

Consequently, the absence of retinopathy does not exclude the diagnosis of DN in patients with type 2 diabetes.

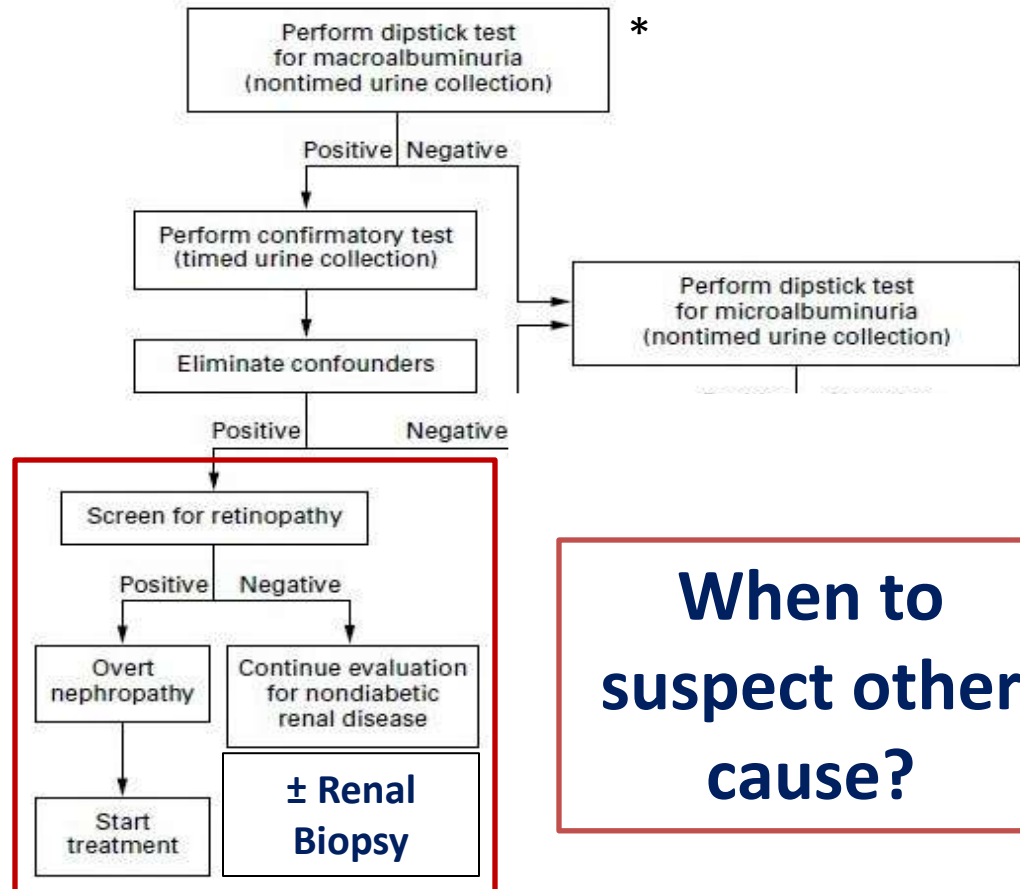
In type 2 DM the prevalence of nondiabetic renal disease could vary from 12 to 38% ***

When to suspect other cause****?

- 1- Younger patients with DM
- 2- Short duration of DM
- 3- Atypical presentation (atypical proteinuria or hematuria, rapid rising Cr etc) or other ppt factors (discussed later)



The NEW ENGLAND
JOURNAL of MEDICINE



**When to
suspect other
cause?**

* GIUSEPPE REMUZZI et al. N Engl J Med, Vol. 346, No. 15· April 11, 2002

** Wolf G, Müller N, Mandecka A, Müller UA. Clin Nephrol. 2007;68:81-86.

*** Huang F et al. Clin ephrol 2007, 67: 293-297.

**** Pham TT et al. Am J Nephrol. 2007;27:322-328.



Is Fluorescein Angiography Safe in Diabetics with Renal Impairment?

OBSERVATIONS

Renal Function Following Fluorescein Angiography in Diabetic Patients With Chronic Kidney Disease



Among consecutive diabetic patients undergoing fluorescein angiography to assess retinopathy at the Department of Ophthalmology, Diabetic Center, Tokyo Women's Medical University Hospital, between 1 August 2003 and 31 August 2008, those who had serum creatinine measurements at both baseline (within 30 days before fluorescein angiography) and follow-up (within 30 days after fluorescein angiography) were identified. Finally, patients with an estimated glomerular filtration rate (eGFR) at baseline <60 ml/min per 1.73 m² were studied. Upon fluorescein angiography, 2.5 ml of 10% sodium fluorescein solution was injected into the antecubital vein over

23.5 ± 5.0 and 23.5 ± 6.2 ml/min per 1.73 m² for 28 patients with stage 4 CKD ($P = 0.991$), and 10.1 ± 4.1 and 10.1 ± 4.3 ml/min per 1.73 m² for 10 patients with stage 5 CKD ($P = 0.870$).

The current study showed that in diabetic patients with CKD, eGFR did not change significantly following fluorescein angiography at any CKD stage, suggesting that fluorescein hardly affects renal function even in diabetic patients carrying a greater risk of a significant loss in kidney function. Prospective studies will be required to confirm these results and determine whether fluorescein angiography is associated with higher incidence of adverse effects in CKD patients.

Is Fluorescein Angiography Safe in Diabetics with Renal Impairment?

Effect of fluorescein on renal function among diabetic patients

Nefrologia 2011;31(5):612-3

doi:10.3265/Nefrologia.pre2011.Jun.10945



been published about the iodinated contrast media induced nephropathy¹⁻³, there is a few researches about renal injury secondary to fluorescein (as a noniodinated contrast media)⁴. In this investigation, we have been tried to evaluate effect of fluorescein sodium on the renal function among diabetic patients who have more susceptible to the renal injury compared with general population⁵.

and female, 1.05 ± 0.40 ; $p = 0.60$), and after angiography was 1.16 ± 0.08 mg/dl (male, 1.23 ± 0.62 and female, 1.11 ± 0.50 ; $p = 0.49$). Nine patients (20.5%) had an increase in SCr from baseline within 72 hours of fluorescein administration (7 male and 2 female).

In the present study, we did not observe any significant adverse effects after fluorescein usage.

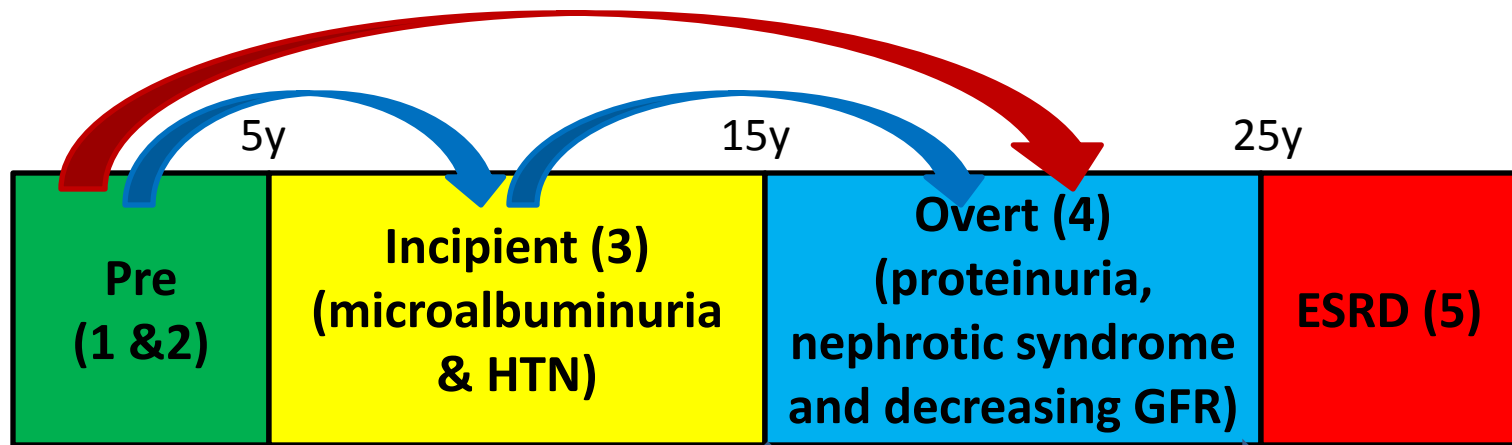
Is it Diabetic Nephropathy?

You have to answer the following

3. Proteinuria:

- a. Is the evolution of proteinuria is typical (micro then macro)?
- b. Is the range of proteinuria coincides with DN stage?
- c. What is the rate of proteinuria progression?

Diabetic Nephropathy & Proteinuria



If evolution of proteinuria is atypical: development of overt proteinuria without previous microalbuminuria.

10-15 years

Overt proteinuria in diabetes type 1 for <10 years



Rate of proteinuria progression is slow

If the onset of proteinuria has been sudden and rapid



Search for other cause of nephropathy rather than DM ± Renal Biopsy (especially if there is S&S of other systemic disease)

DN without Albuminuria

Ischemic Nephropathy – Type 2 DM

- Renal ultrasound reveals small kidneys.
- Raised Serum Cr after administration of ACE-i
- Without albuminuria

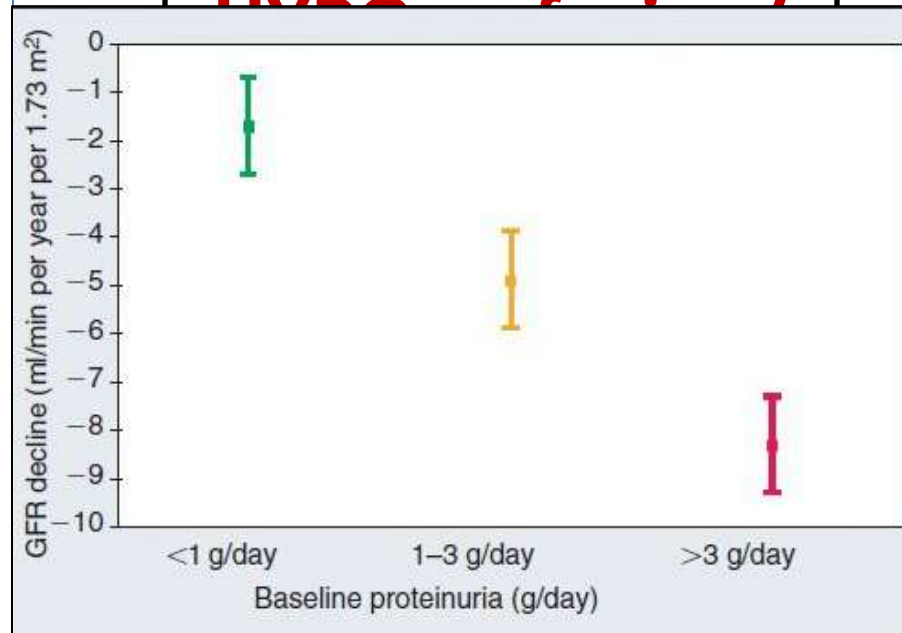
HYPERperfusion/ Hyperfiltration

Hyperglycemia

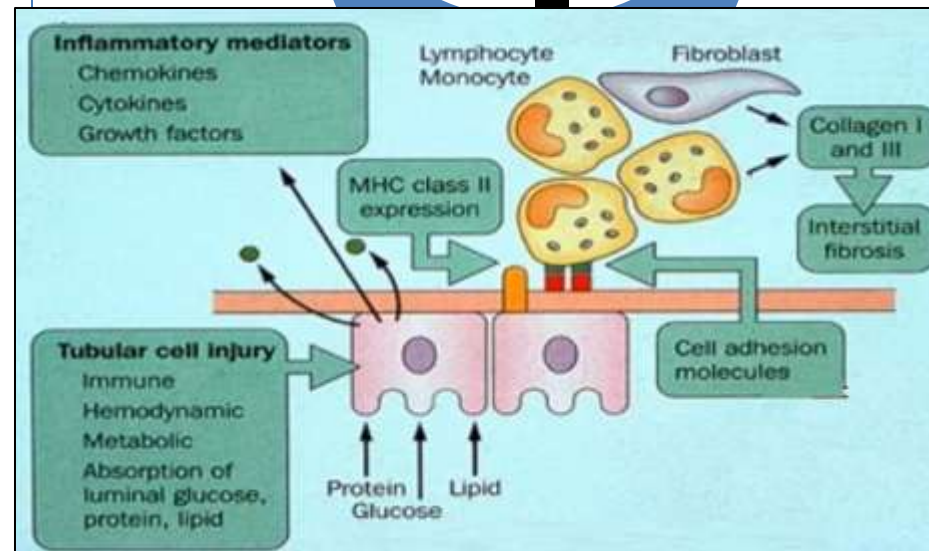
Angiotensin II

↑
Intraglomerular
Pressure

Proteinuria



J Am Soc Nephrol. 2000;14:3217-3232



Renal Dysfunction in the Presence of Normoalbuminuria in Type 2 Diabetes: Results from the DEMAND Study

Jamie P. Dwyer^a Hans-Henrik Parving^{b, c}
Lawrence G. Hunsicker^d Moti Ravid^e Giuseppe Remuzzi^f
Julia B. Lewis^a for the DEMAND Investigators

Table 2. CKD stage and level of albuminuria (A)

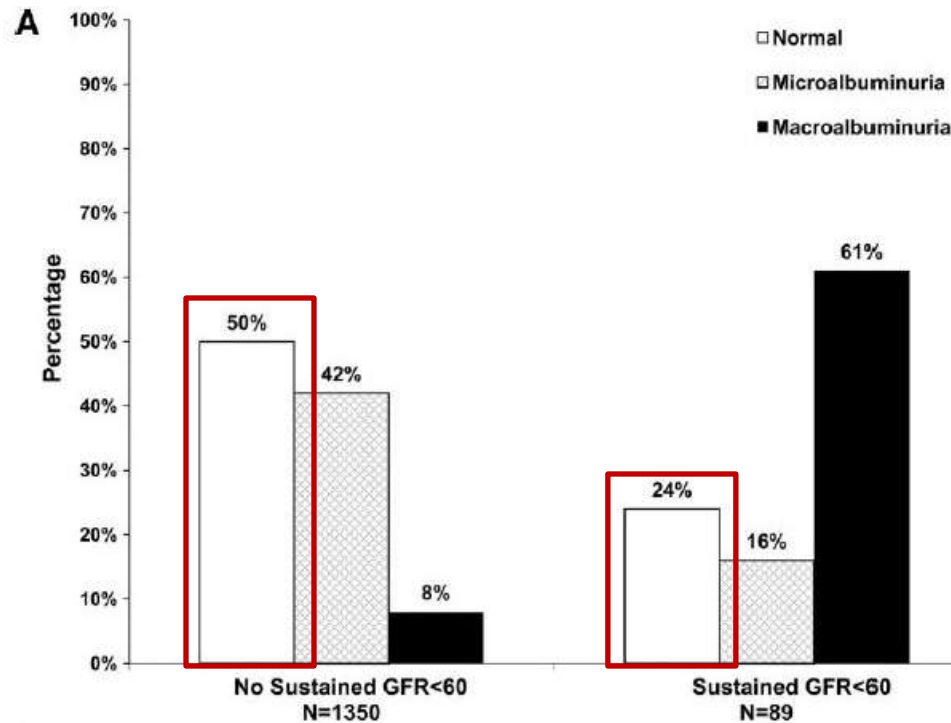
CKD	n	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
Total	24,151 (100%)	51%	39%	10%
Stage 1	3,132 (13%)	56%	36%	8.4%
Stage 2	5,855 (24%)	56%	36%	8.5%
Stage 3	2,428 (10%)	41%	47%	12%
Stage 4	141 (0.6%)	26%	48%	26%
Stage 5	17 (0.07%)	29%	47%	24%
Unknown	12,578 (58%)	51%	39%	10%

CKD stage was classified according to MDRD and NKF criteria. Total includes even those patients in whom measures of kidney function were not obtained (categorized as Unknown). In a total of 11,573 patients, data to calculate kidney function were available.

DN without Albuminuria - Type 1 DM

Development and Progression of Renal Insufficiency With and Without Albuminuria in Adults With Type 1 Diabetes in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Study

American Diabetes Association. Diabetes Care



- MARK E. MOLITCH. Diabetes Care 33:1536–1543, 2010
- Also same results are reported in:
 - Caramori ML et al. Diabetes 52:1036-1040, 2003.
 - Lane PH et al. Diabetes 41:581-586, 1992
 - MacIsaac RJ et al. Diabetes Care 27:195-200, 2004



Is it Diabetic Nephropathy?

You have to answer the following

4. Hematuria: Is it microscopic or macroscopic?

Diabetic Nephropathy & Hematuria

Is it Micro or Macroscopic?

Hematuria in diabetic patient

Microscopic hematuria is seen in 66% of patients with DN *

Red blood cell casts have also been described in patients with **diabetic nephropathy** **

* Akimoto T, Ito C, Saito O, et al. Nephron Clin Pract. 2008; 109:c119-c126.

** Lopes de Faria et al. Clin Nephrol. 1988;30(3):117

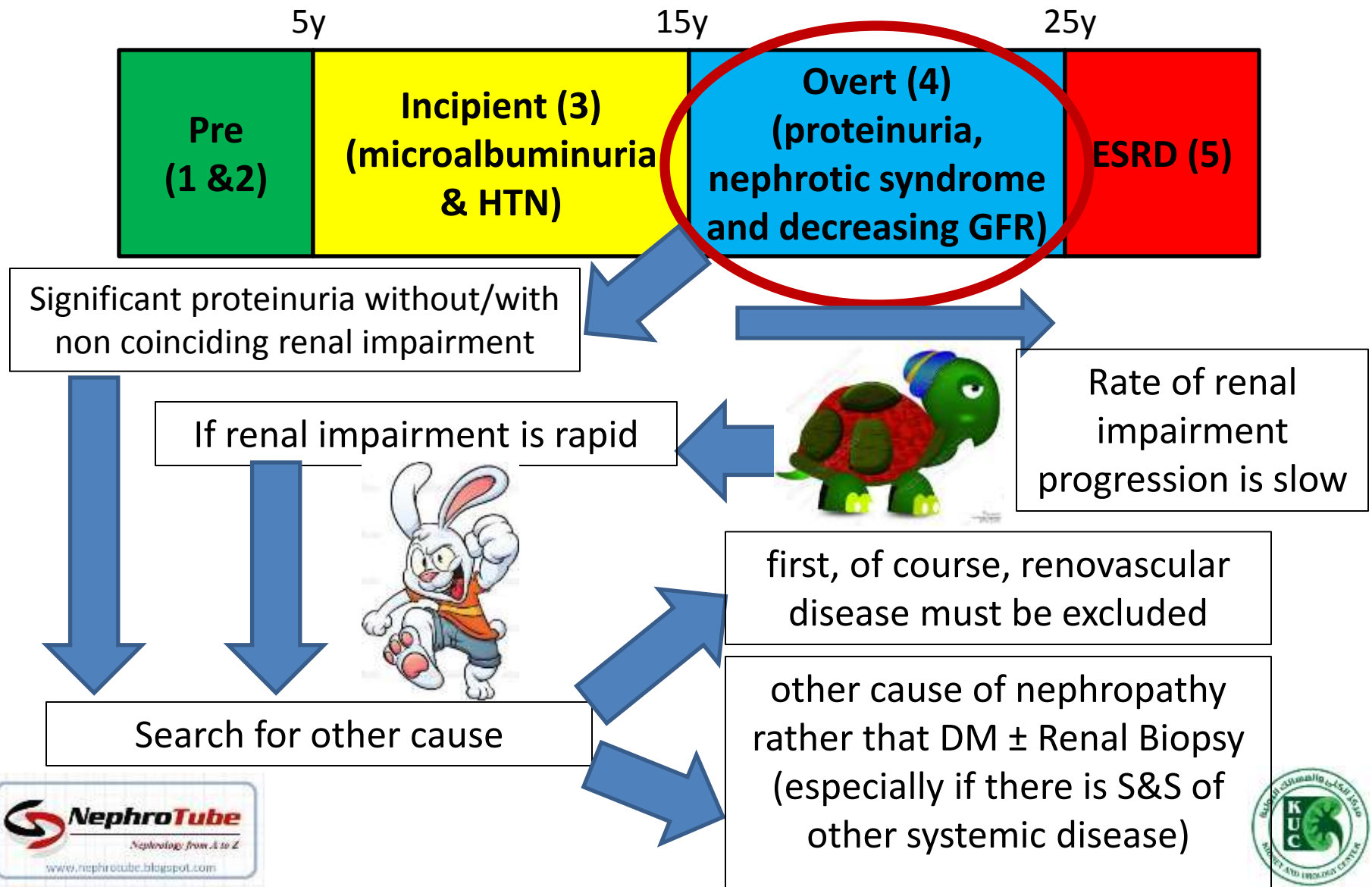
Is it Diabetic Nephropathy?

You have to answer the following

5. Rising Cr and decreasing GFR:

- a. Is it related to proteinuria?
- b. What is the rate of renal impairment progression?

Diabetic Nephropathy & Renal Impairment



Is it Diabetic Nephropathy?

You have to answer the following

6. Hypertension: refractory or not?

Diabetic Nephropathy & Refractory HTN

Refractory hypertension (*and fluid retention*) in diabetic patients is highly suggestive for **renovascular disease**

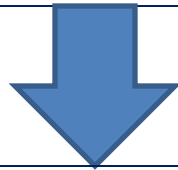
Is it Diabetic Nephropathy?

You have to answer the following

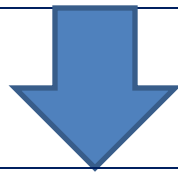
7. What is the drug history?

Diabetic Nephropathy & Drugs

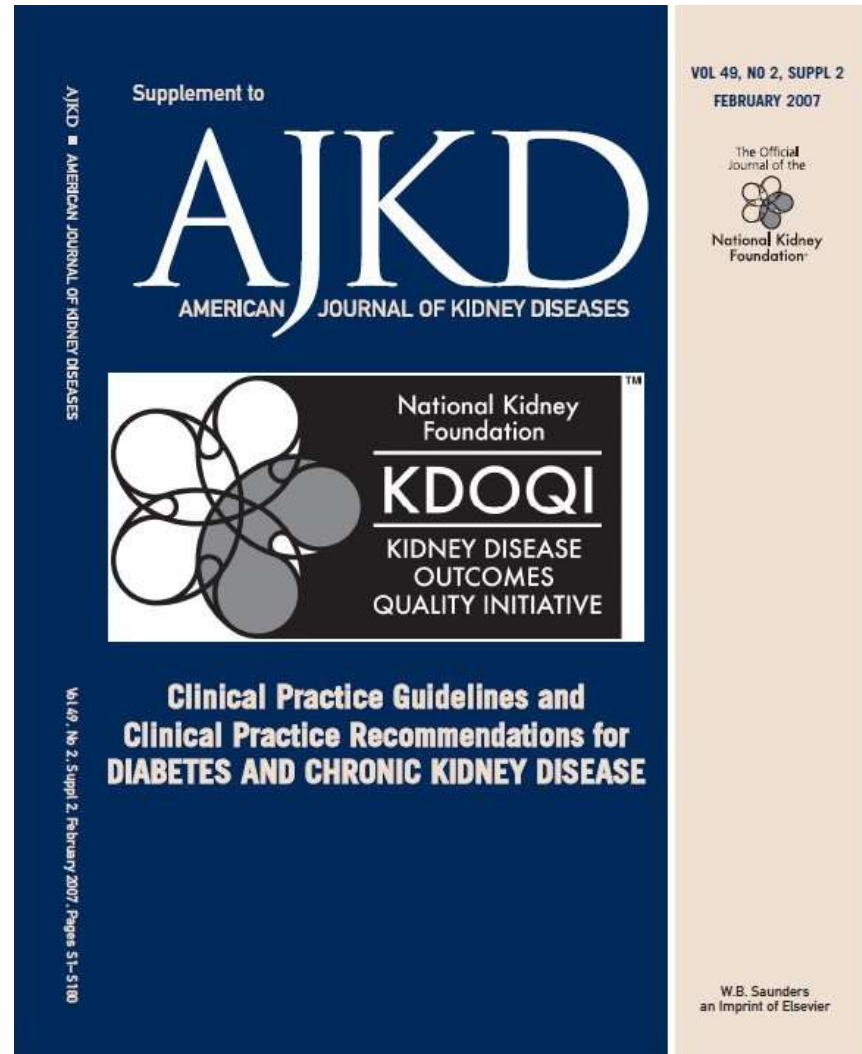
ACEi & ARBs



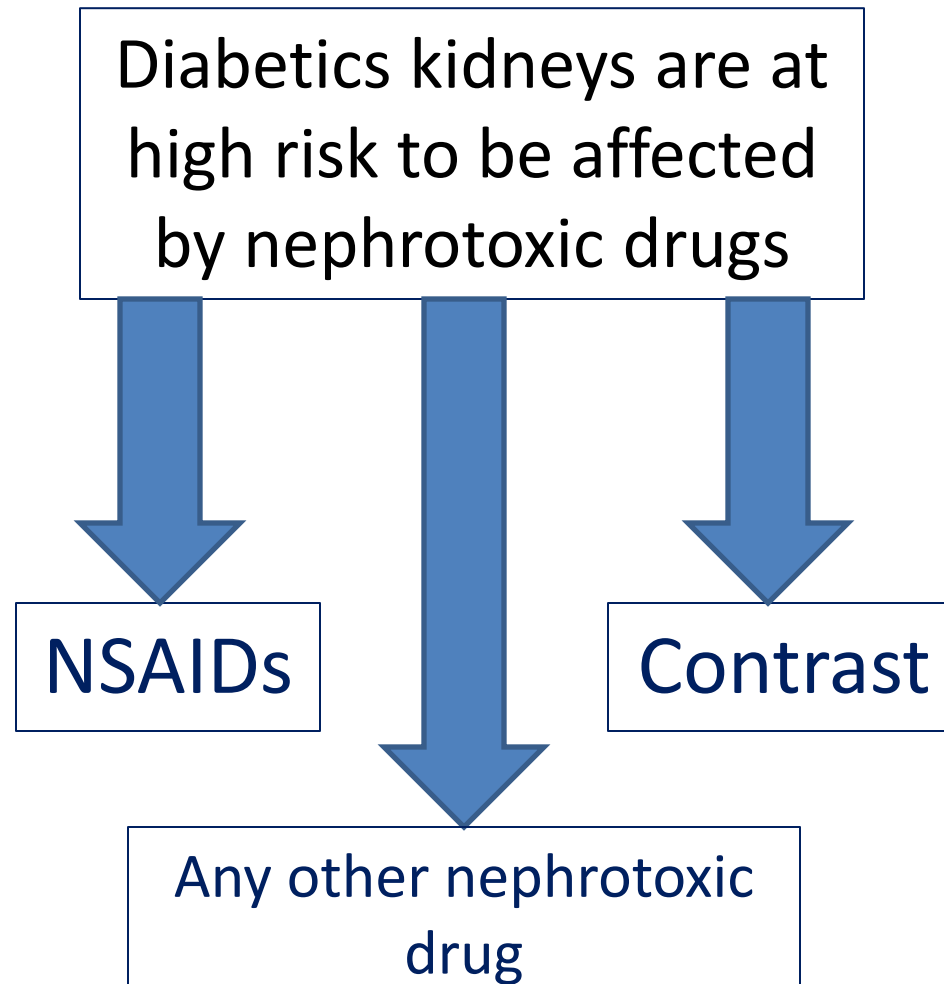
> 30% reduction in GFR
within 2-3 months after
initiation



Suspect renovascular
disease



Diabetic Nephropathy & Drugs



Is it Diabetic Nephropathy?

You have to answer the following

8. Is there any ppt factor for AKI?

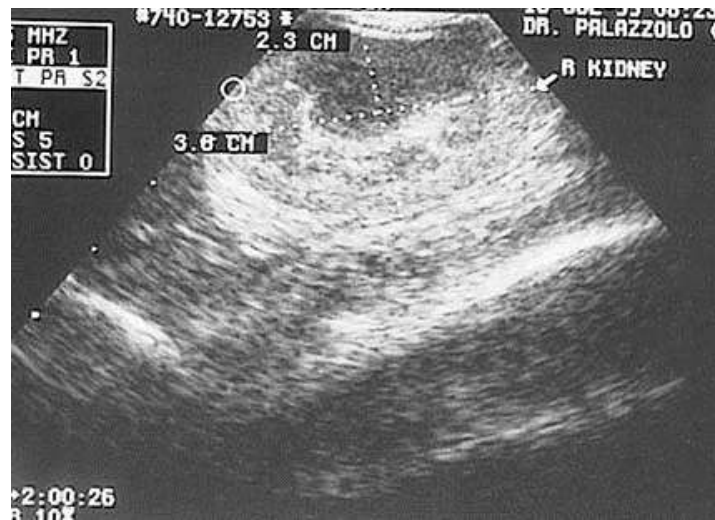
ppt factors for AKI in Diabetics

They are the same as any high risk population

1. Dehydration (fluid loss, hyperglycemia, decrease fluid intake).
2. UTI.
3. Drugs.
4. Cardiac problem.
5. Septicemia.
6. Surgery.

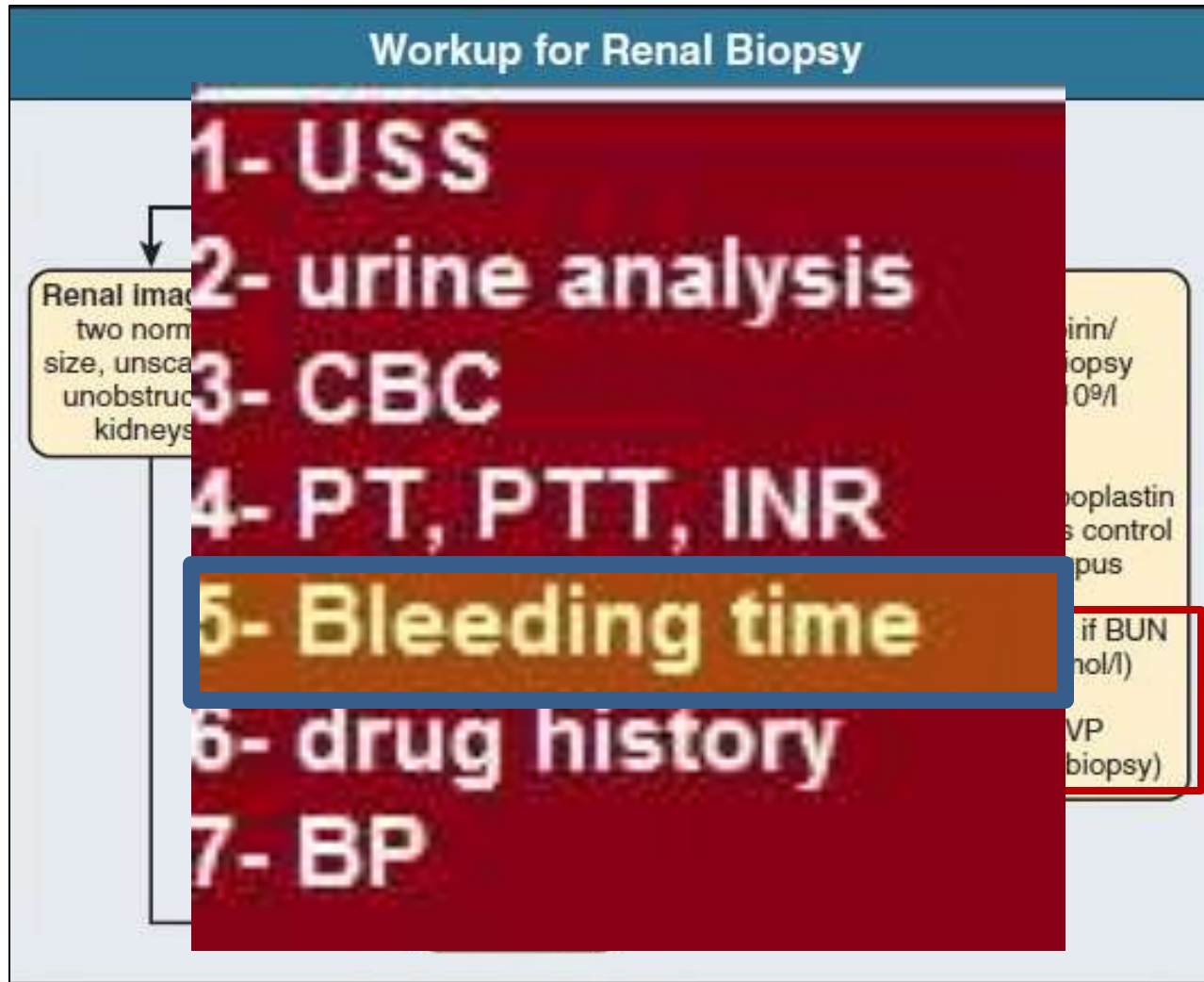
USS & Renal Biopsy

- If renal ultrasound reveals small kidneys it is prudent not to perform biopsy.



- Overall, renal biopsy is indicated only in a small minority of diabetic patients.

USS & Renal Biopsy



Pathology

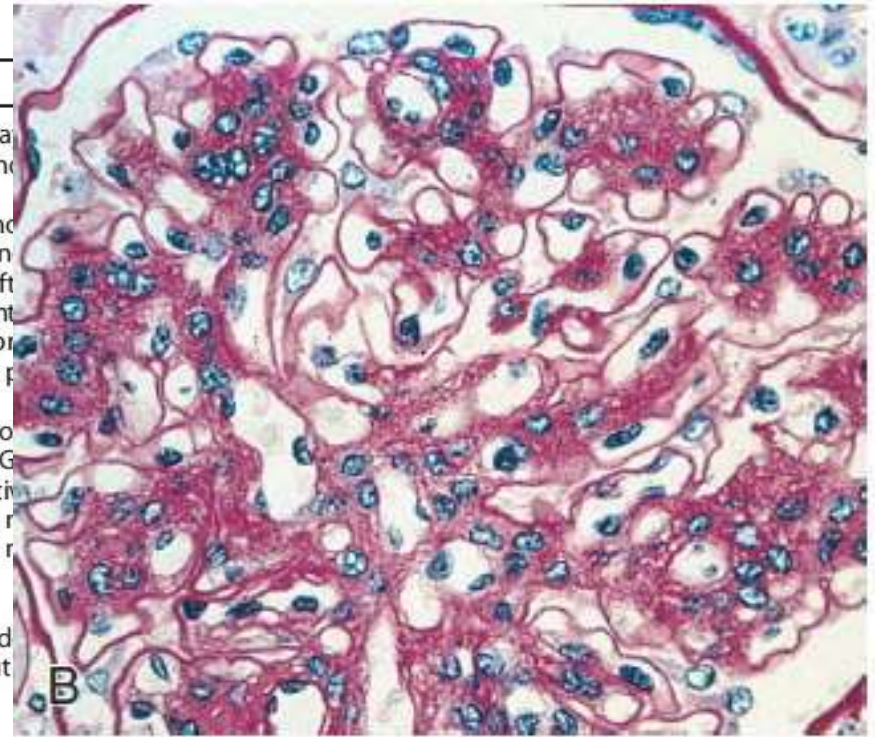
Pathology - Nodular

Pathology - Diffuse

Table 1 | Differential diagnosis of nodular glomerulosclerosis

Entity	Clinical	LM
ING	No history of DM	Nodules may be frequent and larger than DM
Nodular diabetic glomerulosclerosis	History of DM	Scattered nodules in mesangial n (1-2 per tuft) Double contour cellularity present Congo red positive
Membranoproliferative glomerulonephritis (primary or secondary)	Etiology dependent	
Amyloidosis (AL or AA)	Etiology dependent	
Monoclonal Ig deposition disease	Paraprotein in blood and/or urine	Nodules more frequent than DM and ING Jones positive Congo red negative
Fibrillary glomerulonephritis	Usually unexpected	
Immunotactoid glomerulonephritis	Paraproteinemia or lymphoproliferative disorder	
Fibronectin glomerulopathy	Family history	Mesangial deposits positive but
Type III collagen glomerulopathy	Blood and urine N-terminal procollagen type III peptide	May be hypercellular

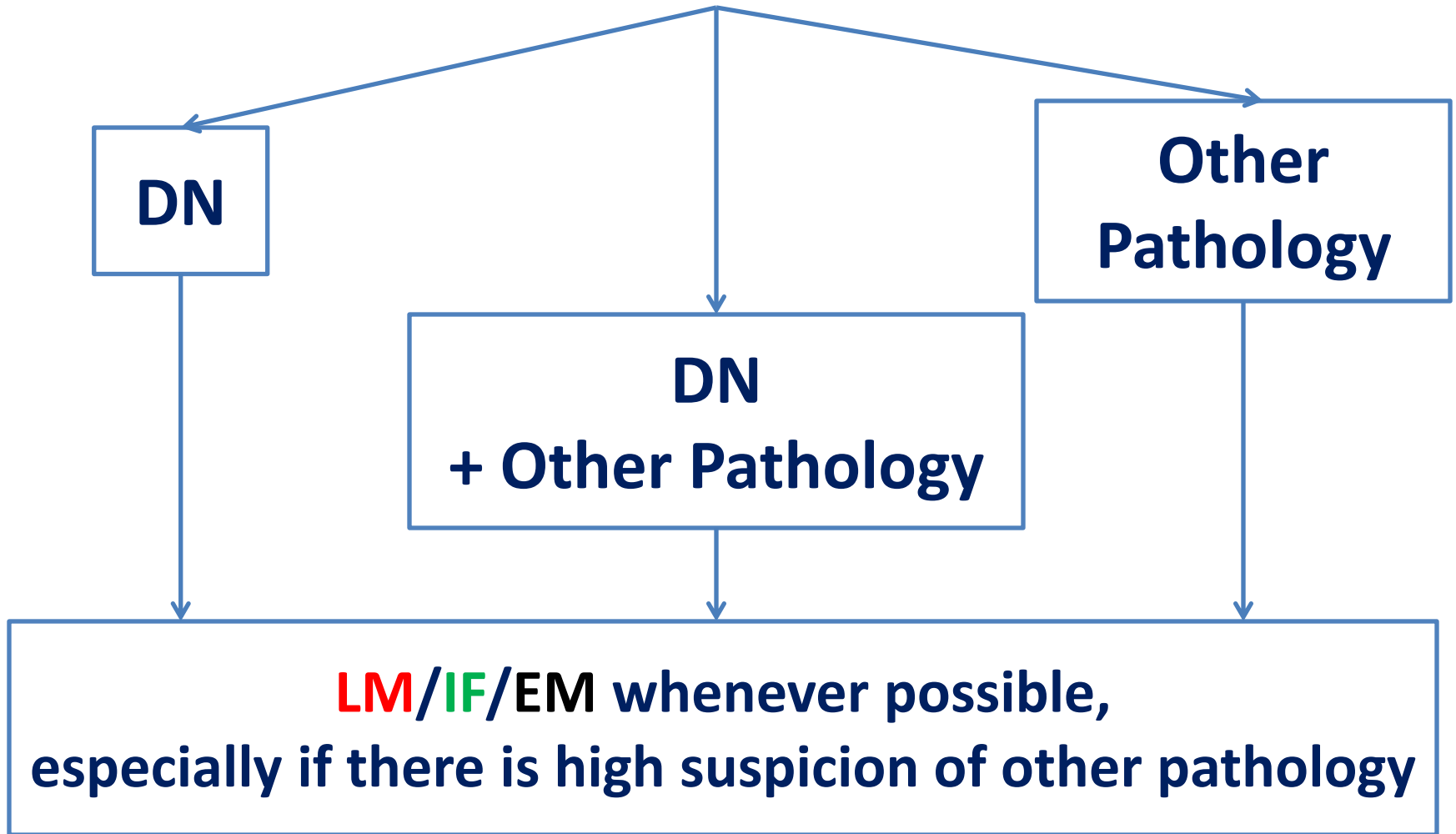
Abbreviations: AA, amyloid associated; AL, amyloid light chain; DM, diabetic mellitus; IF, immunofluorescence; Ig, immunoglobulin; ING, idiopathic nodular glomerulonephritis.



sits
3

- MORE FREQUENT than the nodular lesion
- Correlates with the clinical manifestations
of worsening renal function

Pathology



To Conclude

To Conclude

Diabetes & Kidney Scenarios

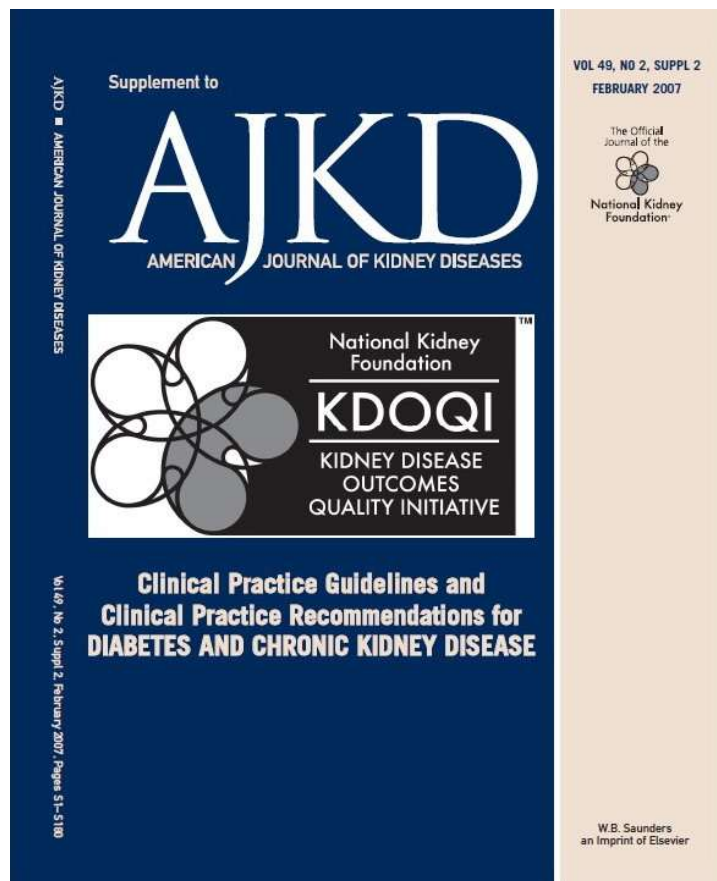
Diabetic with
recent discovered
renal problem

Due to DN

Not due to DN

To Conclude

When to suspect other Cause(s) of Renal Disease rather than DN? (Is it DN?)

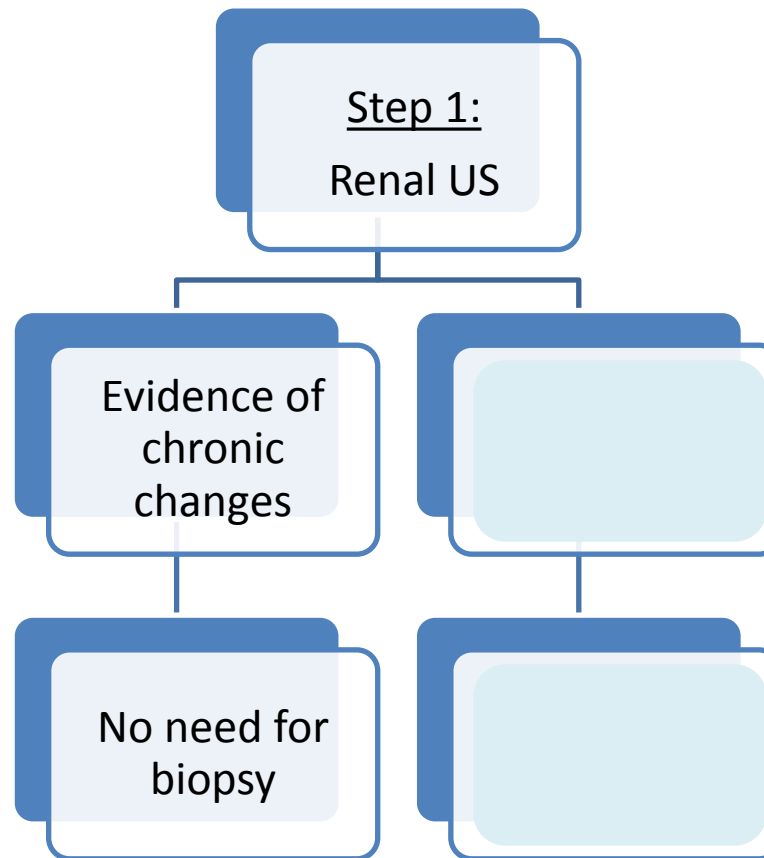


1.4 Other cause(s) of CKD should be considered in the presence of any of the following circumstances: (B)

- Absence of diabetic retinopathy;
- Low or rapidly decreasing GFR;
- Rapidly increasing proteinuria or nephrotic syndrome; !!!!!!!
- Refractory hypertension;
- Presence of active urinary sediment;
- Signs or symptoms of other systemic disease; or
- >30% reduction in GFR within 2-3 months after initiation of an ACE inhibitor or ARB.

To Conclude

When to suspect other Cause(s) of Renal Disease rather than DN? (Is it DN?) – Step 1



To Conclude

When to suspect other Cause(s) of Renal Disease rather than DN? (Is it DN?) – Step 2

	Suspect other cause rather than DN if:
<u>Diabetic retinopathy</u>	<ul style="list-style-type: none">- Absent in Type 1- Absent in type 2 +<ul style="list-style-type: none">1- Short duration of DM2- Atypical presentation or other ppt factors

Case 1

Case Study: A 57-Year-Old Man With Type 2 Diabetes, Hypertension, and Microalbuminuria

Jeffrey A. Luerding, MD

Is it DN?

Presentation

R.C. is a 57-year-old man with type 2 diabetes first diagnosed 2 years ago. Other medical problems include obesity and hypothyroidism. He has a history of heavy alcohol use but quit drinking alcohol 2 years ago. He presents now for routine follow-up and is noted to have a blood pressure of 168/100 mmHg. He is asymptomatic.

Physical exam reveals a height of 5 feet, 8 inches, weight of 243 lb, blood pressure of 160/100 mmHg, and a regular pulse of 84 beats/min. There is no retinopathy or thyromegaly. There is no clinical evidence of congestive heart failure or peripheral vascular disease.

Laboratory evaluation reveals trace protein on urinalysis, blood urea nitrogen of 14 mg/dl, serum creatinine of 1.2 mg/dl, random serum glucose of 169 mg/dl, normal electrolytes, and normal thyroid-stimulating hormone levels. A 24-h urine collection reveals a urinary albumin excretion rate of 250 mg/day.

Case Study: Renal Disease in Type 1 Diabetes

William H. Herman, MD, MPH

C.M. is a 27-year-old woman with type 1 diabetes diagnosed at age 14 when she presented with diabetic ketoacidosis. Her initial insulin treatment was complicated by poor glycemic control, frequent hypoglycemia, and weight gain.

Two years ago she developed hypertension, which was treated with hydrochlorothiazide, 25 mg daily. At that time, she was noted to have nonproliferative diabetic retinopathy. Blood urea nitrogen (BUN) was 23 mg/dl, creatinine was 0.9 mg/dl, and dipstick urinalysis was negative for protein.

Is it DN?
Would you biopsy?

She now presents with accelerated hypertension (172/108 mmHg) and pitting edema of the legs to the level of the knees. Urinalysis reveals 3+ protein and 2+ blood. Urine microscopic analysis reveals hyalin and red blood cell casts. BUN is 37 mg/dl; creatinine is 1.5 mg/dl; and 24-h urine reveals 9.7 g of protein. Creatinine clearance is 58 ml/min. Total cholesterol is 279 mg/dl.

Case 2

cont

Case Study: Renal Disease in Type 1 Diabetes

William H. Herman, MD, MPH

On further testing, Westergren erythrocyte sedimentation rate was 81 mm/h, urine immunoelectrophoresis was negative for Bence Jones protein, and rheumatoid factor was negative, but antinuclear antibody was positive in a titer of 1:320 with a homogenous pattern. Anti-DNA was 5.1% (normal 0–7%). C3 complement was low, C4 complement was normal, and CH 50 was at the lower limit of normal. Renal biopsy demonstrated mixed proliferative and focal membranous glomerulonephritis consistent with lupus nephropathy. In addition, changes were present suggestive of early diabetic glomerulosclerosis.

A 75-YEAR-OLD MAN WITH DIABETIC NEPHROPATHY

Ralph Rabkin, MD

MEDICAL HISTORY

The patient was diagnosed with type 2 DM in 1995 and has had hypertension for more than 20 years. He had transient ischemic attacks in 2002 and 2003. He also suffers from gastroesophageal reflux disease and osteoarthritis of the knees. The patient is currently taking the following daily medications:

PHYSICAL EXAMINATION

At presentation, the patient appeared to be alert, well oriented, and obese. Physical examination indicated the following results: weight, 228 lbs; height, 67 inches; BP, 140/85 mm Hg; pulse rate, 71/min. Extremities, 2 plus peripheral edema was present. No skin rashes were apparent. Funduscopic examination revealed no evidence of diabetic retinopathy. His chest was clear to auscultation. His heart rate and rhythm were within the reference ranges, with a soft grade 1 ejection murmur. No jugular venous distention and no carotid bruits were detected. His abdomen was obese, but no abnormalities were evident.

Is it DN?
Would you biopsy?

LABORATORY FINDINGS

Findings from the ultrasound examinations of the kidneys and postvoid bladder were within reference ranges. Urine dipstick showed proteinuria (4+). No abnormal sediment was observed in the urinalysis. Spot urine albumin/creatinine ratio was determined to be 3 g albumin/g creatinine. Hemoglobin A_{1c} was 7.0; hemoglobin was 11.5 g/dL. Current blood serum/plasma concentrations were evaluated as follows: sodium, 137 mEq/L (normal); potassium, 5.6 mEq/L (high); chloride, 109 mEq/L (high); carbon dioxide, 22 mEq/L (low); glucose, 55 mg/dL (low); creatinine, 2.7 mg/dL (high); blood urea nitrogen, 55 mg/dL (high); and albumin 3.9 mg/dL (Table).

A 75-YEAR-OLD MAN WITH DIABETIC NEPHROPATHY

—
Ralph Rabkin, MD

chloremic acidosis, and proteinuria. The profile is consistent with diabetic nephropathy. However, because of the absence of retinopathy, it is appropriate to consider other common causes of proteinuric renal disease with bland urinary sediment. In this age group, in a patient with anemia, dysproteinurias should be excluded and a urinary protein immunoelectrophoresis should be requested. Other causes of proteinuric nephropathy with bland urinary sediment to be considered in this age group include focal glomerulosclerosis, membranous nephropathy, minimal change disease, immunoglobulin A nephropathy, and nephrosclerosis. Obstructive uropathy has been excluded by ultrasound examination. In most instances, a renal biopsy would be required to definitely establish the renal diagnosis, but based on the chronic nature and severity of the patient's renal impairment, age, and general condition, a renal biopsy will not be considered. The hyperkalemia and

Case 4

The Case | Proteinuria in a patient with diabetes

Srikanth Kunaparaju¹, Chidi Okafor¹, Helen Cathro², Vijay Bhola³, F. Jackson Ballenger⁴ and Mitchell H. Rosner¹

A 49-year-old Caucasian man with type 2 diabetes, hypertension, hyperlipidemia and obesity, and no known renal disease presented with 2 weeks of headache and visual disturbances, and a 6-month history of frothy urine. Diabetes had been diagnosed 3 years previously and had been under excellent control; the most recent Hgb A1c was 7.1%. There was no history of end-organ involvement secondary to diabetes, including retinopathy and neuropathy. Serum and urine protein electrophoresis with immunofixation demonstrated no monoclonal proteins. There was no family history of kidney disease or malignancy.

On examination, the patient's body mass index was 43 kg/m², blood pressure was 230/100 mmHg, and the heart rate was 88/min and regular. The rest of the physical examination was significant for mild periorbital edema and bilateral, 1+ pitting

ankle edema. Laboratory testing showed a serum creatinine of 4.55 mg/dl (baseline a year previously was 1.22 mg/dl), blood urea nitrogen of 38 mg/dl, and a 24-h urine total protein excretion of 10.0 g. Urine microscopy showed 1–2 epithelial cells/high-power field, but no dysmorphic erythrocytes, cellular casts, or crystals. Serological studies including anti-nuclear antibody, anti-ds DNA, anti-neutrophil cytoplasmic antibody, anti-glomerular basement antibodies, complement levels (C3, C4), and HIV, hepatitis B and C viral studies were all within the reference ranges or negative. Serum and urine protein electrophoresis was negative for monoclonal proteins. A renal ultrasound revealed normal-sized kidneys, normal echogenicity bilaterally, and patent renal vasculature. A renal biopsy was performed for diagnosis. Light microscopic findings are depicted in Figure 1.

**Is it DN?
Would you biopsy?**

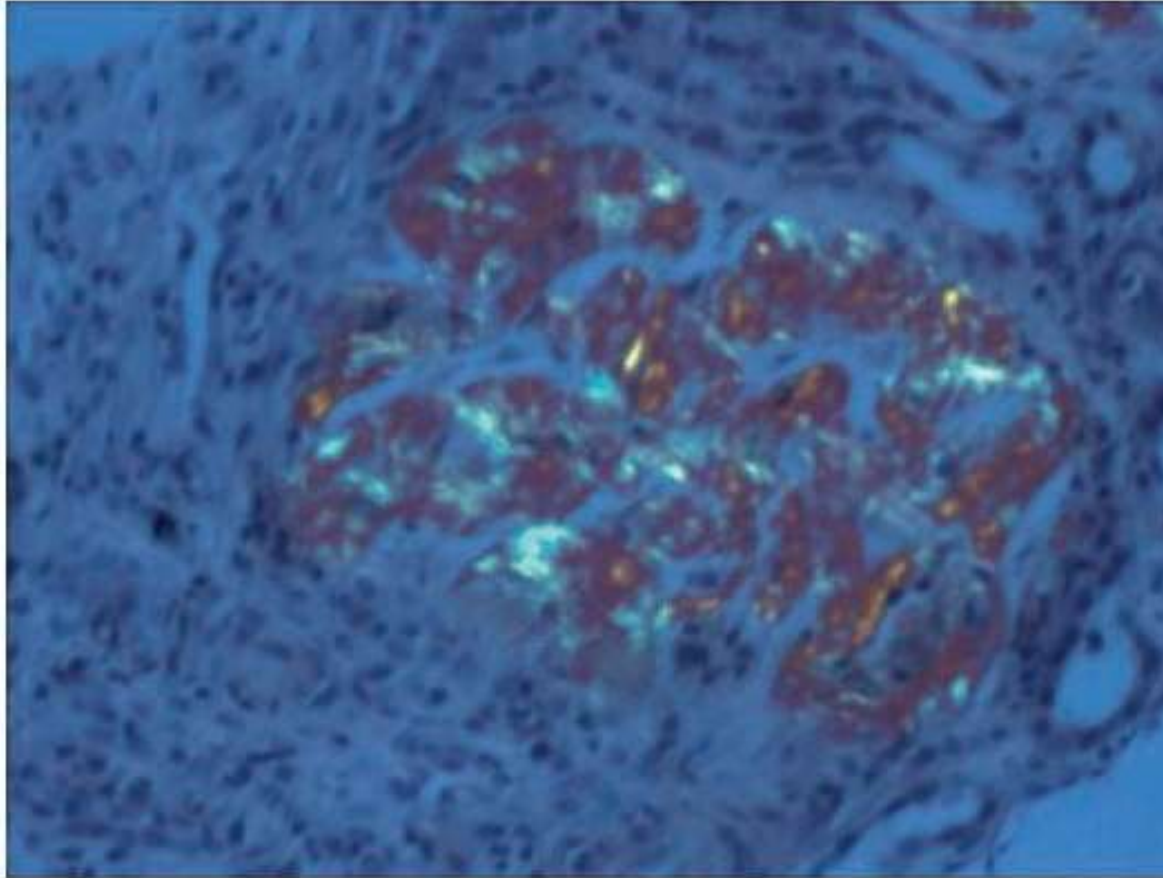
Case 4

Cont

Kidney International (2011) **79**, 793–794;



The Case | Proteinuria in a patient with diabetes



The Diagnosis | Hereditary fibrinogen A α amyloidosis

Figure 2 | Specific apple green birefringence on Congo red staining seen in all glomeruli, but neither in the vascular walls nor in the interstitium.

Take Home Message



Hematuria

Proteinuria

Rising creatinine

Others

- Renal diseases in diabetic patients are **NOT** **ALWAYS** due to diabetic nephropathy and even it may not be due to DM.

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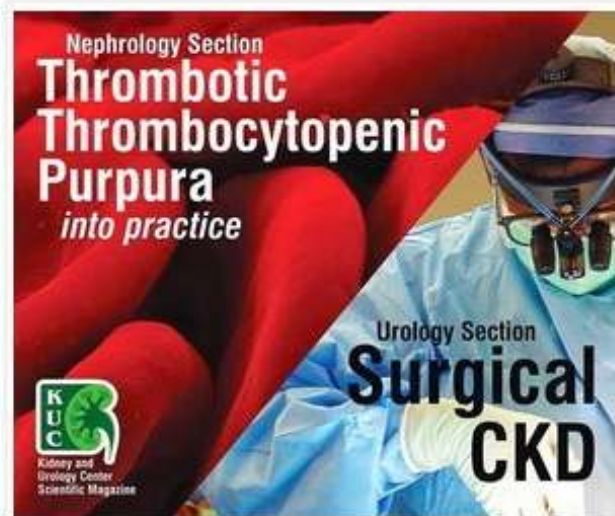
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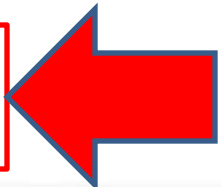
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Thank you!

Mohammed Abdel Gawad